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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,858	08/29/2001	Jorge Plutzky	81994/282421	5046

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EXAMINER

CHANNAVAJJALA, LAKSHMI SARADA

ART UNIT PAPER NUMBER

1615

DATE MAILED: 08/04/2003

12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/940,858

Applicant(s)

PLUTZKY ET AL.

Examiner

Lakshmi S Channavajjala

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12-16 and 24-30 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12-16 and 24-30 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____. 6) ☐ Other: _____

DETAILED ACTION

Receipt of amendment B dated 5-13-03 is acknowledged.

Claims 12-16 and 24-30 are pending.

The following rejection of paper # 10 has been maintained:

Claims 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shaish et al (J. Clin. Invest. 1995; hereafter referred to as Shaish) alone OR Shaish in view of Samokyszyn et al (J. Biol. Chem. 1987; hereafter referred to JBC).

Shaish teaches that oxidatively damaged low-density lipoproteins play an important role in atherogenesis and showed that all-trans isomers of beta-carotene inhibited the formation of atherogenic lesions. Further, Shaish teaches that the metabolites of all-trans-forms of beta-carotene inhibit atherosclerosis. Shaish does not teach the oxidized all-trans or oxidized 9-cis-retinoic acid as claimed in the instant claims. Shaish does not teach the claimed dosages of the compounds.

JBC studied the hydroperoxide-dependent oxidation of 13-cisretinoic acid in microsomes by prostaglandin synthase and teaches the major oxygenated metabolites such as 4-hydroxy, 5,6-epoxy, 5,8-oxy-13-cis –retinoic acid etc. Further, JBC teaches isomerization of all-trans –retinoic acid to 13-cis configuration has been observed during oxidative metabolism to the 4-oxo metabolite (page 14129). JBC further teaches that oxidation products of cis-retinoic acid and all trans-retinoic acid are effective in scavenging free radicals, (in the context of lipid peroxidation as well as tumor promotion) and further suggest that epoxide retinoic acids may actually represent a pharmacologically active form of retinoic acid and even further, hydroperoxide-dependent cooxidation of 13-cis-retinoic acid by prostaglandin synthase represents a

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metabolic activation. While JBC does not teach the specific oxidized retinoic acid compounds claimed, it would have been obvious for one of an ordinary skill in the art at the time of the instant invention to use oxidized forms of cis- or all-trans isomers of retinoic acid for the treatment of atherosclerosis because JBC teaches that epoxy products (a result of oxidation) of cis-retinoic or trans retinoic acids represent the metabolically active forms of retinoic acid. Accordingly, one of an ordinary skill in the art would have used oxidized retinoic (cis as well as trans) in the teachings of Shaish, with an expectation to inhibit lipid peroxidation and in turn inhibit atherosclerosis. Further, it would have been within the scope of a skilled artisan to use appropriate amounts of oxidized retinoic acids with an expectation to achieve the art recognized effect.

This rejection is also applied to the new claims 24-30. Claims 24-29 are directed to a method of preventing the formation of atherosclerotic lesions in patients undergoing heart transplantation, comprising administering an effective amount of compound selected from the group consisting of oxidized all-trans retinoic acid, oxidized 9-cis retinoic acid and reduced 4-oxo-retinoic acid. With respect to the term “preventing” applicants’ attention is directed to the new rejection of claims as non-enabled under 35 USC 112, 1st paragraph. The new claims are rejected as being obvious over Shaish et al and Samokyszyn et al for the reasons described in the above paragraphs.

The following is a new rejection of claims 24-29:

Claim Rejections - 35 USC § 112

Claims 24-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating a patient for atherosclerosis, does not reasonably provide enablement for preventing the formation of atherosclerotic lesion. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Instant specification describes a method of treating a patient for atherosclerosis, diabetes, underweight etc., using various oxidized forms retinoic acid. The specification teaches various dosages of administration by different routes for treating the conditions. However, the specification fails to teach or describe how to prevent the formation of atherosclerotic lesion. In the instant only states that the claimed compounds can be administered before or after or during heart transplantation. However, the specification does not teach as to the conditions that require such prevention in heart transplant patients or how long the treatment with the claimed compounds last so as to prevent the development completely. Besides, applicants also failed to teach or describe the specific symptoms or markers that denote the complete prevention of the development of an atherosclerotic lesion. Instant specification also fails to state or teach if any such standard practices known in the art. Furthermore, instant specification fails to describe or exemplify the claimed method of prevention. Thus, in the absence of any guidance as to the duration of administration or the end point determination associated with the completion of prevention of the atherosclerosis, one of an ordinary skill in the art would

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have to perform undue experimentation in order to determine the requirement for such as prevention in a patient undergoing heart transplantation, the duration of treatment and the termination of the treatment to ensure the prevention is complete and effective.

Response to Arguments

Applicant's arguments filed 5-13-03 have been fully considered but they are not persuasive.

Applicants argue that Shaish teaches a specific type of scavenging activity of beta-carotene that involves a specific receptor-ligand interaction and not a generalized one and that one cannot draw a reasonable conclusion from Shaish that involves all the metabolites. Further, applicants state that nothing in the teaching of Shaish suggests that would require the metabolite responsible for activity be a direct breakdown product of beta-carotene. Applicants' arguments are considered but not found persuasive because instant claims only recite a method of treating a patient with atherosclerosis but does not any specific mechanism in the treatment. Thus, applicants' argument that the effect of beta-carotene in Shaish is unrelated to the oxidation is not pertinent. Examiner notes that the rejection stated such based on the abstract of Shaish, in the previous action. However, a complete reference is attached with this action. Further, while Shaish does not teach any specific metabolite of beta-carotene, the teachings of Shaish suggests that beta-carotene or its metabolites play a role in inhibiting atherogenesis (page 2080, col. 1, 2nd paragraph). Further, Shaish teaches that retinoic acid receptor is activated by both all-trans beta-carotene and 9-cis-retinoic acid raising the possibility that the genes specifically controlled by retinoic acid receptor inhibit atherosclerosis. Thus, the

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teachings of Shaish are suggestive of the role of beta-carotene and retinoic acid as well as their metabolites in atherosclerosis.

Applicants argue that the suggestion of Samokyszyn that active forms of retinoic acid are oxidized is found in reference to the article of Wertz et al, which is limited in scope and does not extend to atherosclerosis. However, the relevance and the suggestion of retinoic acid to atherosclerosis comes from Shaish itself (page 2080, col. 1) and therefore argument regarding the teaching of Wertz et al is not pertinent to instant claims. Further, Samokyszyn teaches several oxygenated metabolites of 13-cis-retinoic acid including 4-hydroxy-13-cis retinoic acid, 4-oxo-retinoic acid, 4-oxo-all trans retinoic acid as well as 5-epoxy, 4-hydroxy, 5,8-oxo-13-cis-retinoic acid are observed upon cooxidation of 13-cis-retinoic acid. Thus, Samokyszyn teaches various oxygenated metabolites that include the claimed oxidized forms of retinoic acid, which would be expected to activate retinoic acid receptor and thus its role in atherogenesis. Therefore, one of an ordinary skill in the art would have expected the metabolites taught by Samokyszyn to be effective in treating a patient for atherosclerosis.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within

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TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S Channavajjala whose telephone number is 703-308-2438. The examiner can normally be reached on 7.30 AM -4.00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on 703-308-2927. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-7924 for regular communications and 703-308-7924 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Lakshmi S Channavajjala
Examiner
Art Unit 1615
July 30, 2003



THURMAN K PAGE
SUPERVISORY PATENT EXAMINER
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